

INFORMATION DISCLOSURE  
CITATION

APPLN. NO.

ATTY. DKT. NO.

10/537,545

5192-16

APPLICANT

ZLOKOVIC et al.

FILING DATE

GROUP

December 18, 2006

1649

## U.S. PATENT DOCUMENTS

*EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	FILING DATE		
				CLASS	SUBCLASS	IF APPROPRIATE
	4,981,952	01/1991	Yan			
	5,321,123	06/1994	Griffin et al.			
	5,405,946	04/1995	Griffin et al.			
	5,663,142	09/1997	Bouma et al.			
	5,804,181	09/1998	Eibl et al.			
	5,891,843	04/1999	Turecek et al.			
	6,008,199	12/1999	Grinnell et al.			
	6,130,201	10/2000	Croce et al.			
	6,756,208	06/2004	Griffin et al.			
	7,204,981	04/2007	Ciaccia et al.			
	7,498,305	03/2009	Griffin et al.			
	2003/0073632	04/2003	Ciaccia et al.			
	2004/0132688	07/2004	Griffin et al.			
	2005/0037964	02/2005	Griffin et al.			
	2007/0042961	02/2007	Griffin et al.			
	2007/0142272	06/2007	Zlokovic et al.			
	2007/0142293	06/2007	Ciaccia et al.			
	2008/0305100	12/2008	Zlokovic et al.			

## FOREIGN PATENT DOCUMENTS

TRANSLATION

DOCUMENT	DATE	COUNTRY	CLASS	SUBCLASS	YES	NO
93/09807	05/1993	WO				
01/56532	08/2001	WO				
2004/030619	04/2004	WO				
2004/056309	07/2004	WO				
2005/007820	01/2005	WO				
2006/014839	02/2006	WO				
2008/055145	05/2008	WO				

## OTHER DOCUMENTS (including Author, Title, Pertinent pages, Date, etc.)

	Abraham et al. "Assessment of the safety of recombinant tissue factor pathway inhibitor in patients with severe sepsis: A multicenter, randomized, placebo-controlled, single-blind, dose escalation study" <i>Crit. Care Med.</i> 29:2081-2089 (2001)
	Arosio et al. "Mutation of W215 compromises thrombin cleavage of fibrinogen, but not of PAR-1 or protein C" <i>Biochemistry</i> 39:8095-8101 (2000)
	Balazs et al. "Endothelial protein C receptor (CD201) explicitly identifies hematopoietic stem cells in murine bone marrow" <i>Blood</i> 107:2317-2321 (2006)
	Berg et al. "Engineering the proteolytic specificity of activated protein C improves its pharmacological properties" <i>Proc. Natl. Acad. Sci. USA</i> 100:4423-4428 (2003)
	Bernard et al. "Safety and dose relationship of recombinant human activated protein C for coagulopathy in severe sepsis" <i>Crit. Care Med.</i> 29:2051-2059 (2001)
	Bernard et al. "Efficacy and safety of recombinant human activated protein C for severe sepsis" <i>New Engl. J. Med.</i> 344:699-709 (2001)

\*Examiner \_\_\_\_\_ Date Considered \_\_\_\_\_

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INFORMATION DISCLOSURE		APPLN. NO.	ATTY. DKT. NO.
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APPLICANT			
(Use several sheets if necessary)		ZLOKOVIC et al.	GROUP
FILING DATE		December 18, 2006 1649	
OTHER DOCUMENTS (including Author, Title, Pertinent pages, Date, etc.)			
<p>Chase &amp; Shaw "p-Nitrophenyl-p'-guanidinobenzoate HCl: A new active site titrant for trypsin" <i>Biochem. Biophys. Res. Comm.</i> 29:508-514 (1967)</p> <p>Cheng et al. "Activated protein C inhibits tissue plasminogen activator-induced brain hemorrhage" <i>Nature Med.</i> 12:1278-1285 (2006)</p> <p>Conway et al. "The lectin-like domain of thrombomodulin confers protection from neutrophil-mediated tissue damage by suppressing adhesion molecule expression via nuclear factor <math>\kappa</math>B and mitogen-activated protein kinase pathways" <i>J. Exp. Med.</i> 196:565-577 (2002)</p> <p>Edgell et al. "Permanent cell line expressing human factor VIII-related antigen established by hybridization" <i>Proc. Natl. Acad. Sci. USA</i> 80:3734-3737 (1983)</p> <p>Esmon "The anticoagulant and anti-inflammatory roles of the protein C anticoagulant pathway" <i>J. Autoimmun.</i> 15:113-116 (2000)</p> <p>Esmon "Regulation of blood coagulation" <i>Biochim. Biophys. Acta</i> 1477:349-360 (2000)</p> <p>Esmon "The endothelial cell protein C receptor" <i>Thromb Haemost.</i> 83:639-643 (2000)</p> <p>Esmon "Protein C pathway in sepsis" <i>Ann. Med.</i> 34:598-605 (2002)</p> <p>Feistritzer et al. "Protective signaling by activated protein C is mechanistically linked to protein C activation on endothelial cells" <i>J. Biol. Chem.</i> 281:20077-20084 (2006)</p> <p>Fisher et al. "Models of the serine protease domain of the human antithrombotic plasma factor activated protein C and its zymogen" <i>Protein Sci.</i> 3:588-599 (1994)</p> <p>Friedrich et al. "Secondary substrate-binding exosite in the serine protease domain of activated protein C important for cleavage at Arg-506 but not at Arg-306 in factor Va" <i>J. Biol. Chem.</i> 276:23105-23108 (2001)</p> <p>Friedrich et al. "Structural and energetic characteristics of the heparin-binding site in antithrombotic protein C" <i>J. Biol. Chem.</i> 276:24122-24128 (2001)</p> <p>Fukudome &amp; Esmon "Molecular cloning and expression of murine and bovine endothelial cell protein C/activated protein C receptor (EPCR). The structural and functional conservation in human, bovine, and murine EPCR" <i>J. Biol. Chem.</i> 270:5571-5577 (1995)</p> <p>Gale et al. "Nonenzymatic anticoagulant activity of the mutant serine protease Ser360Ala-activated protein C mediated by factor Va" <i>Protein Sci.</i> 6:132-140 (1997)</p> <p>Gale et al. "The autolysis loop of activated protein C interacts with factor Va and differentiates between the Arg506 and Arg306 cleavage sites" <i>Blood</i> 96:585-593 (2000)</p> <p>Gale et al. "Molecular characterization of an extended binding site for coagulation factor Va in the positive exosite of activated protein C" <i>J. Biol. Chem.</i> 277:28836-28840 (2002)</p> <p>Gerlitz &amp; Grinnell "Mutation of protease domain residues Lys37-39 in human protein C inhibits activation by the thrombomodulin-thrombin complex without affecting activation by free thrombin" <i>J. Biol. Chem.</i> 271:22285-22288 (1996)</p> <p>Griffin et al. "Activated protein C: Potential therapy for severe sepsis, thrombosis, and stroke" <i>Semin. Hematol.</i> 39:197-205 (2002)</p> <p>Griffin et al. "The promise of protein C" <i>Blood Cells</i> 36:211-216 (2006)</p> <p>Griffin et al. "Activated protein C" <i>J. Thromb. Haemost.</i> 5:73-80 (2007)</p> <p>Grinnell et al. "Differentiation of cytoprotective vs. anticoagulant function with variants of activated protein C in LPS-induced renal microvascular dysfunction" <i>Crit. Care Med.</i> 35(suppl.):A11, abstract 42 (2007)</p> <p>Grotta et al. "Adding to the effectiveness of intravenous tissue plasminogen activator for treating acute stroke" <i>Circulation</i> 107:2769-2770 (2003)</p> <p>Guo et al. "Species-dependent neuroprotection by activated protein C mutants with reduced anticoagulant activity" <i>J. Neurochem.</i> 109:116-124 (2009)</p> <p>Haley et al. "The activation of bovine protein C by factor Xa" <i>J. Biol. Chem.</i> 264:16303-16310 (1989)</p>			
*Examiner		Date Considered	

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(Use several sheets if necessary)		ZLOKOVIC et al.	GROUP
FILING DATE		December 18, 2006 1649	
OTHER DOCUMENTS (including Author, Title, Pertinent pages, Date, etc.)			
Han et al. "Proteomic analysis of active multiple sclerosis lesions reveals therapeutic targets" <i>Nature</i> 451:1076-1081 (2008)			
Heeb et al. "Inhibition of activated protein C by recombinant $\alpha_1$ -antitrypsin variants with substitution of arginine or leucine for methionine <sup>358</sup> " <i>J. Biol. Chem.</i> 265:2365-2369 (1990)			
Hinds "Treatment of sepsis with activated protein C" <i>Brit. Med. J.</i> 323:881-882 (2001)			
Hotchkiss et al. "The pathophysiology and treatment of sepsis" <i>N. Engl. J. Med.</i> 348:138-150 (2003)			
Idziorek et al. "YOPRO-1 permits cytofluorometric analysis of programmed cell death (apoptosis) without interfering with cell viability" <i>J. Immunol. Meth.</i> 185:249-258 (1995)			
Isobe et al. "Activated protein C prevents endotoxin-induced hypotension in rats by inhibiting excessive production of nitric oxide" <i>Circulation</i> 104:1171-1175 (2001)			
Joyce et al. "Gene expression profile of antithrombotic protein C defines new mechanisms modulating inflammation and apoptosis" <i>J. Biol. Chem.</i> 276:11199-11203 (2001)			
Kalafatis & Mann "Role of the membrane in the inactivation of factor Va by activated protein C" <i>J. Biol. Chem.</i> 268:27246-27257 (1993)			
Kanji et al. "Recombinant human activated protein C, drotrecogin alfa (activated): A novel therapy for severe sepsis" <i>Pharmacother.</i> 21:1389-1402 (2001)			
Kerschen et al. "Endotoxemia and sepsis mortality reduction by non-anticoagulant activated protein C" <i>J. Exp. Med.</i> 204:2439-2448 (2007)			
Kisiel "Human plasma protein C: Isolation, characterization, and mechanism of activation by $\alpha$ -thrombin" <i>J. Clin. Invest.</i> 64:761-769 (1979)			
Knobe et al. "Probing the activation of protein C by the thrombin-thrombomodulin complex using structural analysis, site-directed mutagenesis, and computer modeling" <i>Proteins</i> 35:218-234 (1999)			
Kuliopoulos et al. "Plasmin desensitization of the PAR1 thrombin receptor: Kinetics, sites of truncation, and implications for thrombolytic therapy" <i>Biochemistry</i> 38:4572-4585 (1999)			
Marlar et al. "Mechanism of action of human activated protein C, a thrombin-dependent anticoagulant enzyme" <i>Blood</i> 59:1067-1072 (1982)			
Mather et al. "The 2.8 Å crystal structure of Gla-domainless activated protein C" <i>EMBO J.</i> 15:6822-6831 (1996)			
Mesters et al. "Identification of a sequence of human activated protein C (residues 390-404) essential for its anticoagulant activity" <i>J. Biol. Chem.</i> 266:24514-24519 (1991)			
Mosnier & Griffin "Inhibition of staurosporine-induced apoptosis of endothelial cells by activated protein C requires protease-activated receptor-1 and endothelial cell protein C receptor" <i>Biochem J.</i> 373:65-70 (2003)			
Mosnier et al. "Activated protein C variants with normal cytoprotective but reduced anticoagulant activity" <i>Blood</i> 104:1740-1744 (2004)			
Mosnier & Griffin "Protein C anticoagulant activity in relation to anti-inflammatory and anti-apoptotic activities" <i>Frontiers Biosci.</i> 11:2381-2399 (2006)			
Mosnier et al. "The cytoprotective protein C pathway" <i>Blood</i> 109:3161-3172 (2007)			
Mosnier et al. "Activated protein C mutant with minimal anticoagulant activity, normal cytoprotective activity, and preservation of thrombin activatable fibrinolysis inhibitor-dependent cytoprotective functions" <i>J. Biol. Chem.</i> 282:33022-33033 (2007)			
Nicolaes et al. "Peptide bond cleavages and loss of functional activity during inactivation of factor Va and factor VaR506Q by activated protein C" <i>J. Biol. Chem.</i> 270:21158-21166 (1995)			
Norstrom et al. "Importance of protein S and phospholipid for activated protein C-mediated cleavages in factor Va" <i>J. Biol. Chem.</i> 278:24904-24911 (2003)			
*Examiner		Date Considered	

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**OTHER DOCUMENTS (including Author, Title, Pertinent pages, Date, etc.)**

Oganesyan et al. "The crystal structure of the endothelial protein C receptor and a bound phospholipid" <i>J. Biol. Chem.</i> 277:24851-24854 (2002)
Regan et al. "The endothelial cell protein C receptor. Inhibition of activated protein C anticoagulant function without modulation of reaction with proteinase inhibitors" <i>J. Biol. Chem.</i> 271:17499-17503 (1996)
Riewald et al. "Activation of endothelial cell protease activated receptor 1 by the protein C pathway" <i>Science</i> 296:1880-1882 (2002)
Ritchie et al. "Thrombin inhibits apoptosis of monocytes and plasminogen activator inhibitor 2 (PAI-2) is not responsible for this inhibition" <i>Exp. Cell. Res.</i> 260:20-29 (2000)
Rosing & Tans "Coagulation factor V: An old star shines again" <i>J. Thromb. Haemost.</i> 78:427-433 (1997)
Rothbarth et al. "One single mRNA encodes the centrosomal protein CCD41 and the endothelial cell protein C receptor (EPCR)" <i>FEBS Lett.</i> 458:77-80 (1999)
Russell "Management of sepsis" <i>New Engl. J. Med.</i> 355:1699-1713 (2006)
Sadowski et al. "Vitamin K-dependent carboxylase. Requirements of the rat liver microsomal enzyme system" <i>J. Biol. Chem.</i> 251:2770-2776 (1976)
Shen et al. "Involvement of Lys 62(217) and Lys 63(218) of human anticoagulant protein C in heparin stimulation of inhibition by the protein C inhibitor" <i>J. Thromb. Haemost.</i> 82:72-79 (1999)
Shu et al. "Activated protein C suppresses tissue factor expression on U937 cells in the endothelial protein C receptor-dependent manner" <i>FEBS Lett.</i> 477:208-212 (2000)
Singh et al. "Critical care assessment and management of acute ischemic stroke" <i>J. Vasc. Interven. Radiol.</i> 15:S21-S27 (2004)
Smirnov et al. "A chimeric protein C containing the prothrombin Gla domain exhibits increased anticoagulant activity and altered phospholipid specificity" <i>J. Biol. Chem.</i> 273:9031-9040 (1998)
Stearns-Kurosawa et al. "The endothelial cell protein C receptor augments protein C activation by the thrombin-thrombomodulin complex" <i>Proc. Natl. Acad. Sci. USA</i> 93:10212-10216 (1996)
Taylor et al. "The endothelial cell protein C receptor aids in host defense against <i>Escherichia coli</i> sepsis" <i>Blood</i> 95:1680-1686 (2000)
Theofilopoulos "Systemic lupus erythematosus (SLE), Experimental models" <i>Encyclopedia of Immunology</i> (Roitt & Delves, eds.) Academic Press, pp. 1414-1417 (1992)
Thiyagarajan et al. "Activated protein C promotes neovascularization and neurogenesis in postischemic brain via protease-activated receptor 1" <i>J. Neurosci.</i> 28:12788-12797 (2008)
UniProt: locus ROC_HUMAN, GenBank Accession No. P04070, 22 pages (1986 and updates).
Vasserot et al. "Expanding the clinical utility of therapeutic proteins" Activated protein C variants with improved pharmacological properties" <i>Trends Pharmacol. Sci.</i> 24:501-504 (2003)
Wang et al. "Differential neuroprotection and risk for bleeding from activated protein C with varying degrees of anticoagulant activity" <i>Stroke</i> 40:1864-1869 (2009) and doi:10.1161/STROKEAHA.108.536680 (2008)
Warren et al. "High-dose antithrombin III in severe sepsis: A randomized controlled trial" <i>J. Am. Med. Assoc.</i> 286:1869-1878 (2001)
Weiss et al. "Rapid mapping of protein functional epitopes by combinatorial alanine scanning" <i>Proc. Natl. Acad. Sci. USA</i> 97:8950-8954 (2000)
Yan et al. "Characterization and novel purification of recombinant human protein C from three mammalian cell lines" <i>Biotechnol.</i> 8:655-661 (1990)
Yednock et al. "Prevention of experimental autoimmune encephalomyelitis by antibodies against $\alpha 4\beta 1$ integrin" <i>Nature</i> 356:63-66 (1992)
Zlokovic et al. "Functional recovery after embolic stroke in rodents by activated protein C" <i>Ann. Neurol.</i> 58:474-477 (2005)

*Examiner	Date Considered
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